Correspondence

Respiratory Fluoroquinolones: Differences in the Details

SIR—We would like to both comment on and expand on some of the points raised by Saravolatz and Leggett [1] in their review of the newer fluoroquinolones in the 1 November issue. They noted the increased in vitro potency of these agents against *Streptococcus pneumoniae;* however, the major difference between drugs of this class is their intrinsic activity. Moreover, as recognized by the US Food and Drug Administration (FDA) in their approval statement for gemifloxacin in April 2003, gemifloxacin is the only agent that displays activity against both fluoroquinolone target sites at therapeutically achievable levels. Several studies have confirmed this activity against strains of *S. pneumoniae* that possess genes with fluoroquinolone-resistance mutations of *gyrA, parC,* or both [2, 3]. This property may be important, because, as the authors rightly note, there is a threat of increasing fluoroquinolone resistance even among community isolates of *S. pneumoniae* [4, 5]. Thus, in order to consistently provide the optimal conditions to eradicate or prevent the selection of resistant first-step mutants, it is necessary to use an agent that combines the best pharmacodynamic properties with the lowest MICs against these strains at each of the 2 targets.

In comparing pharmacodynamic parameters, it is important to use data from isolates from the same study and not to merge data from different sources. The FDA package insert data are a consistent benchmark and yield somewhat different pharmacodynamic parameters for *S. pneumoniae* than those reported by Saravolatz and Leggett (table 1) [6–8].

Comparison of clinical responses to the 3 new fluoroquinolones (i.e., gatifloxacin, gemifloxacin, and moxifloxacin) shows some differentiating features between the drugs. Regulatory-agency studies are designed to show noninferiority in comparative clinical trials. All of the regulatory-agency studies that have compared gatifloxacin and moxifloxacin with other fluoroquinolones achieved this goal. In contrast, File et al. [9] reported a comparison of gemifloxacin with trovafloxacin for treatment of community-acquired pneumonia (CAP) in which gemifloxacin was shown to be superior in the intention-to-treat (ITT) population for clinical outcomes. Another stufy showed that gemifloxacin was superior to trovafloxacin in the ITT population of a cohort of patients with acute exacerbations of chronic bronchitis (AECB) [10]. An additional clinical trial that compared gemifloxacin with levofloxacin for the treatment of AECB showed a statistically significant difference in favor of gemifloxacin in long-term clinical success at 6 weeks after the end of therapy. Comparisons of gatifloxacin with levofloxacin for treatment of CAP and comparisons of gatifloxacin with moxifloxacin for treatment CAP or AECB due to the same agent showed only noninferiority [11–14]. Unfortunately, no findings of comparative trials involving gemifloxacin, moxifloxacin, or gatifloxacin have been published.

Finally, we agree with Saravolatz and Leggett [1] that the 3 new fluoroquinolones appear to be safe and as well-tolerated as other antibiotics used in the community. However, we wish to point out that gemifloxacin is associated with a higher rate of rash in females aged <40 years. The rate of rash increases to 1%–2% of patients with 7 days of therapy to >12% with >8 days of therapy. Gemifloxacin is approved only for lengths of therapy of ⩽7 days. The overall rate of drug-related rash is 2.8%. The rash is mild-to-moderate in severity, has little to no impact on daily activities, and disappears on cessation of therapy. More-serious dermatologic reactions, such as Stevens-Johnson syndrome, toxic epidermal

Table 1. Pharmacodynamic parameters of gemifloxacin in comparison with other fluoroquinolones against *Streptococcus pneumoniae*.

Variable	Gemifloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
Dose, mg/day	320	500	400	400
S. pneumoniae MIC_{90} in μg/mL	0.03	1.0	0.5	0.25
AUC:MIC free	97–127	40	82	96
Concentration in lung				
Bronchoalveolar macrophages, mg/L	357	42	138	227
Epithelial lining fluid, mg/L	90	9	12	83
Bronchial mucosa, mg/kg	317	7	12	21

Data from [3, 6–8, 16–18].

necrolysis, or eosinophilic dermatosis, have not been reported. A study involving 1044 volunteers showed that most rashes were similar to those seen in treatment with ampicillin [3].

We wish to conclude by strongly endorsing Saravolatz and Leggett's closing comment, which advocates use of the most appropriate fluoroquinolone in specific infections on the basis of the pathogen most likely to be the cause of the infection, and by supporting Scheld's [15] approach, that the drug with the best pharmacodynamics should be used to treat infection caused by the probable organisms.

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References

1. Saravolatz LD, Leggett J. Gatifloxacin, gemifloxacin, and moxifloxacin: the role of 3 newer fluoroquinolones. Clin Infect Dis **2003**; 37: 1210–5.
2. Heaton VJ, Ambler JE, Fisher LM. Potent antipneumococcal activity of gemifloxacin is associated with dual targeting of gyrase and topoisomerase IV, an in vivo target preference for gyrase, and enhanced stabilization of cleavable complexes in vitro. Antimicrob Agents Chemother **2000**; 44:3112–7.
3. Gemifloxacin (Factive), Package Insert, 2003, Genesoft Pharmaceuticals, San Francisco, CA.
4. Lim S, Bast D, McGeer A, de Azavedo J, Low DE. Antimicrobial susceptibility breakpoints and first-step *parC* mutations in Streptococcus pneumoniae: redefining fluoroquinolone resistance. Emerg Infect Dis **2003**; 9:833–7.
5. Jones RN, Biedenbach DJ, Beach ML. Influence of patient age on the susceptibility patterns of Streptococcus pneumoniae isolates in North America (2000–2001): report from the SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis **2003**; 46:77–80.
6. Gatifloxacin (Tequin), package insert, Bristol-Myers-Squibb Pharmaceuticals, Princeton, NJ, **2003**.
7. Moxifloxacin (Avelox), package insert, Bayer Pharmaceuticals, West Haven , CT, 2003. PI
8. Levofloxacin (Levaquin), package insert , Ortho-McNeil Pharmaceuticals, Raritan, NJ, **2002**.
9. File TM Jr, Schlemmer B, Garau J, Cupo M, Young C, the 049 Clinical Study Group. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: a randomized, double-blind comparison with trovafloxacin. J Antimicrob Chemother **2001**; 48:67–74.
10. Ball P, Wilson R, Mandell L, Brown J, Henkel T, the 069 study group. Efficacy of gemifloxacin in acute exacerbations of chronic bronchitis: a randomized, double-blind comparison with trovafloxacin. J Chemother **2001**; 13: 288–98.
11. Sullivan JG, McElroy AD, Honsinger RW, et al. Treating community-acquired pneumonia with once-daily gatifloxacin versus once-daily levofloxacin. Journal of Respiratory Diseases **1999**; 20(Suppl): S49–S59.
12. Hautamaki D, Bruya T, Kureishi A, Warner J, Church D. Short course 5-day moxifloxacin versus 7-day levofloxacin therapy in the treatment of acute exacerbations of chronic bronchitis (AECB). Today's Therapeutic Trends **2001**; 19;117–36.
13. Ureta J, Ariza H, DeBrito JR, et al. Safety and efficacy of moxifloxacin versus levofloxacin in the treatment of AECB. European Congress of Clinical Microbiology and Infectious Diseases, Istanbul, Turkey, 2001, abstract P864.
14. File TM Jr, Larsen LS, Fogarty CM, et al. Safety and efficacy of sequential (IV to PO) moxifloxacin for the treatment of community-acquired pneumonia in hospitalized patients. Today's Therapeutic Trends **2002**; 19:251–70.
15. Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. Emerg Infect Dis **2003**; 9:1–9.
16. Andrews JM, Honeybourne D, Jevons G, Brenwald NP, Cunningham B, Wise R. Concentrations of levofloxacin (HR355) in the respiratory tract following a single oral dose in patients undergoing fibre-optic bronchoscopy. J Antimicrob Chemother **1997**; 40:573–7.
17. Honeybourne D, Banerjee D, Andrews J, Wise R. Concentrations of gatifloxacin in plasma and pulmonary compartments following a single 400 mg oral dose in patients undergoing fibre-optic bronchoscopy. J Antimicrob Chemother **2001**; 48:63–6.
18. Soman A, Honeybourne D, Andrews J, Jevons G, Wise R. Concentrations of moxifloxacin in serum and pulmonary compartments following a single 400 mg oral dose in patients undergoing fibre-optic bronchoscopy. J Antimicrob Chemother **1999**; 44:835–8.

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Clinical Infectious Diseases 2004; 38:1331–2
 1058-4838/2004/3809-0024$15.00

Reply

Sir—We appreciate the letter from Drs. Mandell, Iannini, and Tillotson [1], who expanded on our purposely brief review [2] of newer fluoroquinolones. We hope to address their concerns in our response.

Mandell et al. [1] contend that intrinsic activity and optimal pharmacodynamics should drive fluoroquinolone choice for *Streptococcus pneumoniae* infections, citing a recent article by Dr. Scheld [3]. However, there is, as yet, no absolute consensus on this issue [4]. Debate continues about which optimal pharmacodynamic parameter to use, how to name it, and what breakpoints to employ [5–9]. The use of a single cutoff value (e.g., MIC^{90}) appears to be inferior to the use of Monte Carlo simulations [10]. It is also widely underappreciated that the variability in pharmacodynamic parameters far exceeds the pharmacokinetic variability. A doubling of the MIC (accepted as equivalent in the microbiology laboratory) halves the AUC:MIC and peak concentration:MIC values. Given this variability, in addition to population pharmacokinetic variability in different studies (we do not accept unpublished package insert data as the gold standard), table 1 in Mandell et al. [1] and table 2 in our article [2] appear to us to be essentially the same. Moreover, although targeting both *gyrA* and *parC* is important, this is not the only mechanism involved in preventing resistance [11].

We do not feel that comparing different clinical trials with differing inclusion and exclusion criteria and differing end points is a valid means of declaring the superiority of one agent over another. As Mandell et al. [1] point out, no comparative trials involving these newer fluoroquinolones yet exist.

We would urge clinicians to consider judicious use of any antibiotic, including fluoroquinolones. Resistance has been correlated to increased use, both for *S. pneumoniae* and enteric pathogens impacted collaterally [12, 13]. There is still room for differences of opinion.

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References

1. Mandell LA, Iannini PB, Tillotson GS. Respiratory fluoroquinolones: differences in the details [letter]. Clin Infect Dis **2004**; 38:1331–2 (in this issue).
2. Saravolatz LD, Leggett J. Gatifloxacin, gemifloxacin, and moxifloxacin: the role of 3 newer fluoroquinolones. Clin Infect Dis **2003**; 37: 1210–5.
3. Scheld, WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. Emerging Infectious Diseases **2003**; 9:1–9.
4. Frothingham R. Quinolone safety and efficacy more important the potency. Emerg Infect Dis **2004**; 10:156–7.
5. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis **1998**; 26:1–10.
6. Drusano GL, Berman AL, Fowler CL, et al. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA **1998**; 279:125–9.
7. Scaglione F, Mouton JW, Mattina R, et al. Pharmacodynamics of levofloxacin and ciprofloxacin in a murine pneumonia model: peak concentration/MIC versus area under the curve/MIC ratios. Antimicrob Agents Chemother **2003**; 47:2749–55.
8. Schentag JJ, Meagher AK, Forrest A. Fluoroquinolone AUIC break points and the link to bacterial killing rates; part 2: human trials. Ann Pharmacother **2003**; 37:1478–88.
9. Mouton JW, Dudley MN, Cars O, et al. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs. Int J Antimicrob Agents **2002**; 19: 355–8.
10. Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. Pediatr Infect Dis J **2003**; 22:982–92.
11. Jumbe N, Louie A, Leary R. Application of a mathematical model to prevent in vivo amplification of antibiotic-resistant bacterial populations during therapy. J Clin Invest **2003**; 112:275–85.
12. Zhanel GG, Patrick K, Nichol KA, et al. Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian respiratory organism susceptibility study 1997–2002. Antimicrob Agents Chemother **2003**; 47:1867–74.
13. Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991–2000. Clin Infect Dis **2003**; 37:1643–8.

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Clinical Infectious Diseases 2004; 38:1332–3

Adverse Effects of Bacille Calmette-Guérin Vaccination in HIV-Positive Infants

SIR—We refer to the recent article by Hesseling et al. [1] on Danish bacille Calmette-Guérin (BCG) vaccine–induced disease in HIV-positive children. Although we do not wish to minimize the importance of exercising caution when administering BCG to HIV-exposed infants, we believe the main conclusion reached by the authors—namely, that "the Danish BCG strain poses a risk for localized and disseminated disease in infants who are infected with HIV" [1, p. 1232]—could imply that Danish BCG is more likely than other strains of BCG to cause disseminated disease in these infants. We contend that one cannot reach this conclusion on the basis of the data presented and because of the limitations of the study, particularly the lack of comparable data on other strains of BCG in HIV-infected children.

The fact that the authors found no isolates of *Mycobacterium bovis* BCG in infants and children immunized with the Tokyo *M. bovis* BCG strain may well relate to characteristics of the South African national immunization program before 2000, as well as to the relative pathogenicity of different BCG strains. Prior to 2000, percutaneous Tokyo *M. bovis* BCG vaccination was used. Kibel et al. [2] and Lunn [3] showed that the vaccination tool and method used led to a negligible number of local reactions and little evidence of penetration, because of blunt, bent, and retracted needles and questionable vaccination techniques. It was concluded that the vaccination device in question "fails to introduce adequate quantities of BCG" [3, p. 272]. If inadequate amounts of the Tokyo *M. bovis* BCG strain were being administered to South African infants between 1992 and 2000, that could be a major factor contributing to the failure to observe disseminated Tokyo BCG disease in these infants.

It is also our contention that the data presented leave room for some diagnostic uncertainty. It is true that patients A and B had intra-abdominal adenopathy, and patients A, B, D, and E all had hepatosplenomegaly. In all these cases, the findings are listed as possible manifestations of BCG disease, but, of course, there are other possible causes of hepatosplenomegaly, including disseminated *Mycobacterium tuberculosis* infection, which was present in patients B and E. Patients A and D did have definite evidence of disseminated BCG disease, as evidenced by isolation of *M. bovis* BCG from gastric washing specimens, but patients B, C, and E appear to have had local axillary adenitis, an adverse reaction to BCG vaccination, without definite evidence of dissemination, which is to be expected in a proportion of infants.

In a similar area of South Africa, we are performing follow-up for infants and children as part of a phase 4, randomized, controlled trial comparing the efficacy of percutaneous and intradermal Tokyo 172 BCG vaccination in the prevention of tuberculosis (TB). At the end of September 2003, a total of 8799 infants of a target number of 12,000 had received the vaccine. Active surveillance for vaccine-associated adverse events has, to date, identified 4 instances of ipsilateral axillary lymphadenitis ("regional disease," according to Talbot's classification; incidence, 0.045%). Blood samples for all 4 infants tested negative for HIV infection. The point is that the Tokyo *M. bovis* BCG strain can also cause severe local adverse reactions.

In addition, 663 infants and children enrolled in the trial who were either contacts of persons with TB or were suspected of having TB were evaluated for possible

tuberculous disease; 24 of these were HIV exposed. Evaluation involved admission to a hospital for obtainment of gastric washing and induced sputum specimens for TB smear and culture. Isolates from all positive TB cultures were then typed using biochemical and molecular techniques. Specimens from 105 patients produced results positive for TB. Six of these patients were HIV exposed. None of the isolates obtained to date has been typed as *M. bovis* BCG.

In the same area, as part of a separate evaluation completed this year, we performed follow-up for 100 HIV-exposed infants at 6-16 weeks of age. Of these 100, we found 16 who were HIV-PCR positive [4]. Approximately 50% of these infants had received vaccination with the Danish *M. bovis* BCG strain at birth; the rest received the Tokyo *M. bovis* BCG strain. None of the 100 infants had any evidence of regional, extraregional, or disseminated BCG disease.

In conclusion, we agree that BCG vaccine may have adverse effects in HIV-positive infants. However, the extent of this problem and the relative risk associated with different BCG strains, inoculation routes, and other variables still needs to be formally evaluated in well-designed, rigorous clinical studies.

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References

1. Hesseling AC, Schaaf HS, Hanekom WA, et al. Danish bacille Calmette-Guérin vaccine–induced disease in human immunodeficiency virus–infected children. Clin Infect Dis **2003**; 37:1226-33.
2. Kibel MA, Hussey G, Marco C, van der Wal L. An evaluation of the "Japanese tool" for percutaneous vaccination with BCG in neonates. S Afr Med J **1995**; 85:988–91.
3. Lunn JA. Evaluation of the "Japanese tool" for percutaneous vaccination with BCG in neonates. S Afr Med J **1996**; 86:272.
4. Hussey G. Evaluation of efficacy of the Worcester pMTCT program: report to Boland Overberg Regional Health Department. Cape Town, **2003**.

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Clinical Infectious Diseases 2004; 38:1333–4
 1058-4838/2004/3809-0026$15.00

Reply

Sir—We appreciate the comments from Hussey et al. [1] regarding our recent article [2]. Our main aim was to determine whether local and systemic complications from bacille Calmette-Guérin (BCG) vaccination do occur in HIV-infected infants. We therefore performed a retrospective study, which obviously has limitations. Our main conclusion was that these complications may occur in HIV-infected infants, and that this phenomenon should be studied in more detail in prospective studies.

Our aim was therefore not to compare adverse effects of different BCG vaccine strains. Only those infants vaccinated with the Danish *Mycobacterium bovis* BCG strain were found to have had BCG-disease complications. The risk and clinical presentation in this group of immunocompromised infants were described.

The reason Hussey et al. [1] propose for our finding of an absence of adverse effects following vaccination with the Tokyo BCG strain may be very plausible. However, differences in reactogenicity between BCG strains, and also between the Tokyo BCG strain and the Danish BCG strain, have been described [3, 4], suggesting that different rates of adverse events may also occur. Prospective, direct clinical comparisons of adverse effects following vaccination with different BCG strains are required to address this issue reliably. However, as intradermal vaccine with the Danish *M. bovis* BCG strain is now uniformly administered to both HIV-exposed and HIV-unexposed infants in South Africa, these findings are relevant.

We concur that clinical findings such as intra-abdominal lymphadenopathy and hepatosplenomegaly may allow variable interpretation, particularly in HIV-infected infants. Confirmation by deep-tissue biopsy was not always possible; therefore, we used the term "probable disseminated BCG disease" [5]. However, as pointed out by Hussey et al. [1], the Danish *M.bovis* BCG strain was detected in gastric aspirates of 2 patients, affirming a possible diagnosis of disseminated disease. Further, we attempted to make a clear distinction between regional disease (e.g., ipsilateral adenitis) and systemic BCG disease.

The consequences of ipsilateral adenitis, as described in 3 patients, are unknown in immunocompromised, HIV-infected infants. However, in 1 patient, the initial presentation of ipsilateral adenitis was followed by systemic BCG disease. We pointed out the importance of clinical awareness and appropriate medical and/or surgical management of local complications. Of note, after the completion of our retrospective study, 2 additional cases of ipsilateral adenitis due to the Danish *M. bovis* BCG strain and 1 case of dual infection with *M. tuberculosis* and BCG were detected in severely immunodeficient, HIV-infected infants. The possible role of coinfection with *M. tuberculosis* was not discussed, as we still have inadequate data. However, immunocompetent infants with ipsilateral adenitis caused by BCG may indeed have a very different or minimal risk following local BCG complications, compared with severely immunodeficient infants

We appreciate that Hussey et al. [1] share important preliminary data from their current, large vaccination studies. However, it is difficult to draw any comparisons between our retrospective hospital-based analysis, which describes Danish BCG-induced complications, and their population-based, randomized field trial,

which primarily aims to compare the efficacy of 2 strategies for administration of the Tokyo *M. bovis* BCG strain. It is important to note that no prevalence or incidence data were calculated in our study, as the reference population was unknown. No attempt was made to describe the efficacy of BCG vaccines in our patients.

Results from our retrospective, hospital-based study cannot be extrapolated to the general HIV-infected pediatric population. Our motivation was to assess whether a more formal assessment of risks associated with BCG vaccination in HIV-infected infants was necessary. On the basis of our findings, we concur with Hussey et al. [1] that controlled, population-based studies are essential to describe the true risk of complications of vaccination with BCG strains in HIV-infected infants at a population level. However, if the risk of systemic complications of BCG vaccination among HIV-infected infants were 1 in 10,000, prospective studies may have too few participants to delineate the risk. Retrospective data therefore remain important.

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References

1. Hussey G, Hawkridge T, Eley B, et al. Adverse effects of BCG vaccination in HIV-positive infants [letter]. Clin Infect Dis **2004**; 38:1333–4 (in this issue).
2. Hesseling AC, Schaaf HS, Hanekom WA, et al. Danish bacille Calmette-Guérin vaccine–induced disease in human immunodeficiency virus–infected children. Clin Infect Dis **2003**; 37:1226–33.
3. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. Bull WHO **1990**; 68:93–108.
4. Fine PEM, Carneiro IAM, Milstien JB, Clements CJ. Issues relating to the use of BCG immunization programmes—a discussion document. Document WHO/V&B/ 99.23. Geneva: WHO, **1999**.
5. Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guérin disease after vaccination: case report and review. Clin Infect Dis **1997**; 24:1139–46.

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Clinical Infectious Diseases 2004; 38:1334–5

Clinical Significance of Hepatitis B Core Antibody Positivity in HCV-Infected and HCV/HIV Coinfected Individuals

Sir—The combination of hepatitis B surface antigen (HBsAg) negativity and hepatitis B core antibody (anti-HBc) seropositivity is traditionally interpreted as indicative of prior hepatitis B virus (HBV) infection with clearance. More recently, it has become apparent that HBV DNA can be detected in serum or hepatic samples from at least some individuals who exhibit this combination. According to a recent publication, hepatitis B virus DNA surface and X regions of the hepatitis B virus genome, as well as covalently closed circular HBV DNA, were detected in 9 of 9 liver biopsy specimens obtained from HBsAg-negative individuals with histories of acute hepatitis B infection (median, 7.2 years before liver tissue analysis) [1]. Clinically apparent hepatitis caused by HBV has been reported in HBsAg-negative and anti-HBc–seropositive individuals after immune reconstitution with human immunodeficiency virus (HIV) antiretroviral therapy [2] and as a result of chemotherapy-induced immune suppression [3–5]. This information demonstrates that, in at least some individuals, the phenomenon of occult chronic HBV infection may become clinically relevant.

The triad of hepatitis C virus (HCV) RNA positivity, HBsAg negativity, and anti-HBc seropositivity is frequently found in the clinical setting, given the shared risk factors for transmission of HBV and HCV infection. It is plausible that in individuals with chronic HCV infection, occult HBV persistence may contribute to higher transaminase levels, increased parenchymal inflammatory changes, and more-advanced stages of liver fibrosis [6]. The quartet of HIV RNA positivity and the 3 markers mentioned above is commonly noted in the clinical setting, as well. It is unclear how HIV coinfection influences these complex interactions.

To address these questions, a cohort of 107 individuals who were positive for HCV by PCR and had results from HIV serological testing, anti-HBc and HBsAg testing, and liver biopsy was identified from among subjects followed-up at the Ottawa Hospital Viral Hepatitis Clinic and the University of Ottawa Health Service clinic. Biopsies were interpreted using the METAVIR system [7]. Twenty-two (21%) subjects were HIV-seropositive, of which 15 (68%) were receiving antiretroviral therapy at the time of biopsy. Baseline transaminase levels, inflammation grade, fibrosis stage, and estimated fibrosis rates (defined as METAVIR fibrosis stage divided by the estimated number of years since onset of infection) [8] were compared between anti-HBc–seropositive and anti-HBc–seronegative individuals (table 1). HCV RNA and aminotransferase levels were higher in anti-HBc–seropositive subjects. Excessive alcohol consumption was not responsible for these differences, by our analysis. The mean fibrosis stage and proportion of subjects with advanced fibrosis was greater in anti-HBc–seropositive subjects. However, the estimated fibrosis rates and inflammation grades were similar between these 2 groups. Of note, liver biopsy findings were consistent with chronic HCV infection and were not typical of the findings associated with chronic HBV infection.

HIV-seropositive individuals with chronic HBV infection (i.e., those who were HBsAg-positive) are known to progress more rapidly to cirrhosis and end-stage liver disease [9, 10]. We predicted

Table 1. Comparison of key variables associated with chronic hepatitis between hepatitis B core antibody (HBcAg)–seropositive and HBcAg-seronegative subjects infected with hepatitis C virus (HCV) or coinfected with HCV and HIV.

Patient group, variable	No. of subjects with data available	HBsAg-seropositive subjects	HBsAg-seronegative subjects	P[a]
All subjects				
Male sex	107	35/51 (69)	46/56 (82)	.10
Estimated years since onset of infection, mean ± SD	105	23.4 ± 11.4	18.6 ± 9.7	.02[a]
Fibrosis status				
METAVIR stage, mean ± SD	107	2.06 ± 1.14	1.64 ± 0.92	.04
METAVIR stage ⩾3	107	15/51 (29)	7/56 (13)	.03[b]
Inflammation grade, mean ± SD	107	1.86 ± 0.76	1.78 ± 0.66	.59
Fibrosis rate, mean ± SD	105	0.145 ± 0.28	0.161 ± 0.29	.78
Liver enzyme levels, U/L				
ALT				
Mean ± SD	107	103 ± 94	100 ± 83	.85
Median	107	82	71	.77[c]
AST				
Mean ± SD	107	83 ± 75	68 ± 50	.21
Median	107	59	48	.19[c]
HCV RNA level, IU × 10^5/mL, mean ± SD	96	8.83 ± 6.86	6.11 ± 5.33	.03
Alcohol intake of >50 g/day				
Currently	106	17/51 (33)	12/55 (22)	.18[b]
Previously	103	28/48 (58)	33/55 (60)	.86[b]
HIV-seropositive subjects, fibrosis status				
METAVIR stage, mean ± SD	22	2.46 ± 1.20	2.00 ± 1.32	.40
METAVIR stage ⩾3	22	7/13 (54)	3/9 (33)	.42[d]
Inflammation grade, mean ± SD	22	2.00 ± 0.71	1.89 ± 0.78	.73
Estimated fibrosis rate, mean ± SD	22	0.176 ± 0.15	0.140 ± 0.12	.55

NOTE. Data are proportion (%) of patients, unless indicated otherwise.
[a] Student's t test, unless indicated otherwise.
[b] χ^2 Test.
[c] Mann-Whitney U test.
[d] Fisher's exact test.

that if HBV lingers in anti-HBc–seropositive and HBsAg-negative subjects, then the manifestations of this occult infection would be most obvious in HCV/HIV coinfected individuals. The estimated fibrosis rate was higher for HIV-infected individuals than for HIV-seronegative subjects (mean rate [± SD], 0.161 [0.13] vs. 0.151 [0.31]). However, the grade, stage, and estimated fibrosis rate did not differ based on anti-HBc status in the 22 HCV/HIV coinfected subjects evaluated (table 1).

The objective of this evaluation was to determine whether markers of chronic HCV infection differed in patients routinely dismissed as chronically HBV infected (i.e., those who were anti-HBc–seropositive and HBsAg-negative). Serum HBV DNA levels could not be measured in our cohort of subjects, because of the retrospective nature of this study. Although the inclusion of serum HBV DNA data would have been ideal, this information was not essential to the classification of our subjects or to the interpretation of our analysis. In reality, a negative serum HBV DNA result cannot be relied on to rule in or to rule out occult infection. The lower limit of detection of routinely used systems is insufficient to detect low-level HBV viremia occasionally present in occult HBV infection. Even with a lower threshold for detection, it is unlikely that many of these HCV-seropositive subjects with suspected occult HBV infection would have been HBV DNA positive [6, 11]. Furthermore, serum HBV DNA positivity is rare even among persons with occult HBV infection proven by liver tissue biopsy [1].

In conclusion, accumulating data raise questions as to whether HBV infection is ever truly cleared. Our analysis suggests that, in HBsAg-negative and anti-HBc–seropositive individuals with chronic HCV, occult HBV infection may linger and contribute to increased HCV RNA and liver enzyme elevation. However, occult HBV infection likely does not produce a greater burden of end-stage liver disease, because the estimated liver fibrosis rate was not higher in HCV-monoinfected or in HCV/HIV coinfected individuals. The influence of this phenomenon on the efficacy of HCV and HIV drug therapies merits further evaluation.

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References

1. Yuki N, Nagaoka T, Yamashiro M, et al. Long-term histologic and virologic outcomes of acute self-limited hepatitis B. Hepatology **2003**; 37:1172–9.
2. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. Clin Infect Dis **2001**; 32:144–8.
3. Iwai K, Tashima M, Itoh M, et al. Fulminant hepatitis B following bone marrow transplantation in an HBsAg-negative, HBsAb-positive recipient: reactivation of dormant virus during the immunosuppressive period. Bone Marrow Transplant **2000**; 25:105–8.
4. Senecal D, Pichon E, Dubois F, Delain M, Linassier C, Colombat P. Acute hepatitis B after autologous stem cell transplantation in a man previously infected by hepatitis B virus. Bone Marrow Transplant **1999**; 24:1243–4.
5. Chazouilleres O, Mamish D, Kim M, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet **1994**; 343:142–6.
6. Torbenson M, Thomas DL. Occult hepatitis B. Lancet Infect Dis **2002**; 2:479–86.
7. Bedossa P, Poynard T. An algorithm for the

grading of activity in chronic hepatitis C. METAVIR Cooperative Study Group. Hepatology **1996**; 24:289–93.
8. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. Multivirc Group. Hepatology **1999**; 30:1054–8.
9. Hadler SC, Judson FN, O'Malley PM, et al. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. J Infect Dis **1991**; 163:454–9.
10. Colin JF, Cazals-Hatem D, Loriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology **1999**; 29:1306–10.
11. Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. J Acquir Immune Defic Syndr **2003**; 34:439–41.

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Clinical Infectious Diseases 2004; 38:1335–7

A Multistate Outbreak of *Salmonella enterica* Serotype Saintpaul Infections Linked to Mango Consumption: A Recurrent Theme

SIR—We read with interest the report of a multistate outbreak of *Salmonella enterica* serotype Newport infection in 1999 by Sivapalasingam et al. [1]. The outbreak was associated with the consumption of mangoes imported from a single farm in Brazil. An environmental investigation at the farm revealed that inadequately chlorinated water was used in the hot water immersion treatment to exterminate fruit fly larvae. At the time, the importance of adequately chlorinating the treatment water had not been recognized [1, 2]. We write to report a second outbreak of *S. enterica* infection associated with consumption of mangoes; however, the serotype in this outbreak was Saintpaul. Also imported, these mangoes were possibly contaminated through a mechanism similar to that described by Sivapalasingam et al. [1].

In March of 2001, the Massachusetts and Connecticut departments of public health reported 19 patients with culture-confirmed *S.* Saintpaul infections. The PFGE patterns of the DNA from these isolates were indistinguishable, suggesting an outbreak. By 31 March 2001, *S.* Saintpaul isolates from 7 additional patients, including residents of California, Delaware, New Jersey, New York, and Rhode Island, were identified. The mean age of patients was 35 years (range, 1–89 years); 48% were female.

To identify risk factors for infection, we conducted a case-control study with 13 cases and 25 controls frequency-matched for age, sex, and city of residence. Telephone interviews were conducted by state health department and Centers for Disease Control and Prevention officials using a standardized questionnaire. Raw mango consumption was the only exposure significantly associated with illness (OR, 28.8; 95% CI, 2.1–888; $P = .003$).

Three patients had adequate purchase records for the US Food and Drug Association (FDA) to initiate a "trace-back" investigation; however, only 1 patient's purchase could be traced beyond the retail seller. This patient's receipt indicated that the mangoes were imported from Peru, but there was inadequate information obtained to complete the trace-back to the farm level.

During an unrelated site-visit to mango-producing regions in Peru, US Animal and Plant Health Inspection Service (APHIS) inspectors noted that producers were using untreated water in the final step of the fruit fly control program (P. C. Witherell, US Department of Agriculture, APHIS-Plant Protection and Quarantine, personal communication). Subsequent to the outbreak of mango-associated *S.* Newport infection in 1999 reported by Sivapalasingam et al. [1], APHIS recommended a concentration of 50–200 ppm chlorine in the water used for the hot water immersion treatment [1]. This change was not published until 2002 [3]. It is likely that the mango producers in Peru had not yet learned of the need to chlorinate the water used for hot water immersion treatment, and a second outbreak occurred before the recommendation became widely adopted.

In conclusion, mangoes were implicated as the vehicle during a multistate outbreak of *S.* Saintpaul in February and March of 2001. These mangoes were likely exposed to inadequately chlorinated water, which may have led to contamination with *S.* Saintpaul. APHIS recommendations currently include using adequately chlorinated water in mango processing for the prevention of fruit fly infestation [3]. As of 1 January 2003, no subsequent foodborne outbreaks have been associated with mangoes. The outbreak we report demonstrates the need for thorough microbiologic evaluation of new methods of food processing prior to their implementation, as Sivapalasingam et al. [1] suggest.

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References

1. Sivapalasingam S, Barrett E, Kimura A, et al. A multistate outbreak of *Salmonella enterica* serotype Newport infections linked to mango consumption: impact of water dip disinfestation technology. Clin Infect Dis **2003**; 37: 1585–90.
2. Bond EJ. Manual of fumigation for insect control. In: Food and Agriculture Organization of the United Nations, ed. Food and Agricultural Organization Plant Production and Protection Paper 54. 2nd ed. **1989**. Available at: http://www.fao.org/inpho/. Accessed 6 November 2002.
3. United States Department of Agriculture–Animal and Plant Health Inspection Services–Plant Protection and Quarantine. USDA-APHIS-PPQ Treatment Manual 02/2002-01 edition. USDA-APHIS-PPQ: **2002**.

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Clinical Infectious Diseases 2004; 38:1337–8

Persistence of Physical Symptoms in and Abnormal Laboratory Findings for Survivors of Severe Acute Respiratory Syndrome

Sir—We performed a cross-sectional study to assess the physical symptoms in and abnormal laboratory findings for survivors of severe acute respiratory syndrome (SARS) at their first follow-up visit after discharge from Princess Margaret Hospital (Hong Kong, China). Sixty-two patients who experienced the onset of SARS symptoms during the period from 18 March 18 2003 through 30 March 2003 were recruited. All patients had pneumonia and positive SARS-associated coronavirus (SARS-CoV) seroconversion. The mean age ($\pm$SD) was 37.07 $\pm$ 12.96 years, the ratio of male subjects to female subjects was 0.82, and the intubation rate was 9.6%. In this cohort, 90.3% of patients received treatment with ribavirin and corticosteroids [1]. The median interval ($\pm$SD) between the onset of SARS symptoms and the first follow-up visit was 6.59 $\pm$ 1.07 weeks.

Symptoms reported at the first follow-up visit included palpitation (45.1% of patients), exertional dyspnea (41.9%), malaise (40.3%), easy forgetfulness (30.6%), chest discomfort (22.5%), hand tremor (21%), dizziness (17.7%), depression (16.1%), myalgia (12.9%), headache (9.6%), diarrhoea (8.1%), cough (8.1%), insomnia (6.5%), and hair loss over the scalp (3.2%). No patient reported sputum production. Patients described palpitation as a paroxysmal, fast heart beat or extra heart beat sensation. A sinus tachycardia with resting heart rate of 100–110 beats/min was identified in 18% of patients complaining of palpitation.

Laboratory findings included the following mean values ($\pm$SD): hemoglobin level, 12.93 $\pm$ 1.42 g/dL; WBC count, $6.71 \times 10^9 \pm 2.00 \times 10^9$ cells/L; neutrophil count, $4.58 \times 10^9 \pm 1.75 \times 10^9$ cells/L; lymphocyte count, $1.51 \times 10^9 \pm 0.46 \times 10^9$ lymphocytes/L; platelet count, $308 \times 10^9 \pm 89.26 \times 10^9$ cells/L; erythrocyte sedimentation rate, 11.86 $\pm$ 14.47 mm/h; albumin level, 42.56 $\pm$ 3.58 g/L; globulin level, 30.58 $\pm$ 3.05 g/L; bilirubin level, 8.67 $\pm$ 5.18 umol/L; alkaline phosphatase level, 83.2 $\pm$ 22.44 U/L; alanine aminotransferase level, 28.9 $\pm$ 13.96 U/L; creatinine kinase level, 104 $\pm$ 268.9 U/L; lactate dehydrogenase level, 242 $\pm$ 64.29 U/L. At the first follow-up visit, 46.7% of patients were found to have a lactate dehydrogenase level of >230 U/L. Abnormal chest radiograph findings were reported by the Department of Radiology for 35.4% of patients. These findings included patchy shadows, linear atelectasis, ground glass appearance, reticular marking, and streaky opacities. There was no significant difference in the rate of exertional dyspnea between patients with and patients without abnormal chest radiograph findings ($P = .51$). For all patients, PCR of urine, nasal, and throat swab samples was negative for SARS-CoV RNA. However, for 1 female patient, PCR of a stool sample obtained 35 days after the onset of SARS symptoms was positive for SARS-CoV RNA. No person who had close contact with that patient after she was discharged from the hospital contracted SARS.

From what we have learned, some SARS survivors still had physical symptoms up to 6 weeks after the onset of SARS symptoms, although their complete blood counts, the results of their liver and renal function tests, and their erythrocyte sedimentation rates were largely normalized. The finding of abnormal lactate dehydrogenase levels may imply that patients still had not fully recovered from SARS-related tissue damage at the first follow-up visit. We should not overlook the effect of therapy with ribavirin and corticosteroids, which might have contributed to the symptoms and to the abnormal laboratory values. Physicians providing care to patients with SARS during the convalescent period should be aware of the possibility of such abnormal findings.

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References

1. Choi KW, Chau TN, Tsang TY, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. Ann Intern Med **2003**; 139:715–23.

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Clinical Infectious Diseases 2004; 38:1338